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REVIEW-THEMED ISSUE

Evidence for the impact of interventions and medicines reconciliation on problematic polypharmacy in the UK: A rapid review of systematic reviews

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This was a rapid review of systematic reviews (SRs) on problematic polypharmacy (PP) in the UK. The commissioner-defined topics were burden of PP, interventions to reduce PP, implementation activities to increase uptake of interventions, and efficient handover between primary and secondary care to reduce PP.

Databases including Medline were searched to June 2019, SR quality was assessed using AMSTAR-2 (A MeaSurement Tool to Assess systematic Reviews) and a narrative synthesis was undertaken.

Except for burden of PP (SRs had to include UK studies), there were no restrictions on country, location of care or outcomes.

Nine SRs were included. On burden, three SRs (including six UK studies) found a high prevalence of polypharmacy in long term care. PP was associated with mortality, although unclear if causal, with no information on costs or health consequences. On interventions, six reviews (27 UK studies) found that interventions can reduce PP, but no effects on health outcomes. On handover between primary and secondary care, one review (two UK studies) found medicine reconciliation activities to reduce medication discrepancies at care transitions reduce PP, although the evidence is low quality. No SRs on implementation activities to increase uptake of interventions were found.

SR quality was variable, with some concerns regarding meta-analysis methods.

Evidence of the extent of PP in the UK, and what interventions to address it are effective in the UK, is limited. Future UK research is needed on the prevalence and consequences of PP, the effectiveness and cost-effectiveness of interventions to reduce PP, and barriers and activities to ensure uptake.

KEYWORDS

evidence-based medicine, health policy, overprescribing, polypharmacy, rapid review, systematic review

1 | INTRODUCTION

Medicines use is increasing in the UK as well as internationally.[1] In England, from 2012/13 to 2015/16, the proportion of people prescribed 5-7 medicines increased by 8% and, in those on 8 or more medicines, by 3%.[2] Extrapolating to the population, this amounts to 4.8 million people on 5-7 medicines and 2.8 million people on 8 or more medicines. Much of this multiple medicine use (ie, polypharmacy) may be appropriate, but some patients may be exposed to problematic polypharmacy, also known as overprescribing. Problematic polypharmacy refers to the use of multiple medicines inappropriately or without the intended benefit.[3] Examples include contraindicated drugs, potential for drug interactions or prescribing a drug that has caused adverse drug reactions in the past.[3]

Problematic polypharmacy is a key area of concern for the NHS and UK policy makers. For example, to address problematic polypharmacy, NHS England announced in 2019 that it is recruiting 200 clinical pharmacists to work in care homes and plans to increase the number of clinical pharmacists working in primary care over the coming years.[4]

In 2018, the UK Secretary of State for Health commissioned the Short Life Working Group (SLWG) on Overprescribing to conduct a Review.[5] The SLWG Review will consider problematic polypharmacy, handover between primary and secondary care, management of repeat prescriptions, digital technologies and social prescribing. Social prescribing is a term used in the UK for a referral to a link worker. The link worker helps people to improve their wellbeing (rather than focusing only on their health) by connecting them to community groups and services.[6] To inform this Review, the Department of Health and Social Care (DHSC) commissioned the present study to summarise the evidence on problematic polypharmacy and propose areas for future research.

The a priori defined topics and associated research questions for the present study, agreed between the DHSC and the Short Life Working Group on Overprescribing, were:

- Burden of problematic polypharmacy: What is the prevalence (and/or incidence), what are the costs to the NHS and what are the health consequences of polypharmacy and problematic polypharmacy in the UK?
- Interventions to reduce problematic polypharmacy: What is the effectiveness of interventions to reduce problematic polypharmacy, with specific focus on deprescribing guidelines, routine data and digital technologies?
- Implementation activities to increase uptake of interventions to reduce problematic polypharmacy: What is the effectiveness of implementation activities to increase the uptake of interventions that reduce problematic polypharmacy, with specific focus on activities to increase shared decision making?
- Efficient handover between primary and secondary care to reduce problematic polypharmacy: What is the effectiveness of medicine reconciliation interventions to reduce discrepancies in medication in people at risk of problematic polypharmacy?

What is already known about this subject

- Problematic polypharmacy is a concern for UK health policy.
- In 2018, the UK Secretary of State for Health commissioned a review into overprescribing in the NHS, including problematic polypharmacy.
- This study informs this review by summarising the existing evidence on problematic polypharmacy and proposing areas for future research.

What this study adds

- Existing systematic reviews include few UK studies on problematic polypharmacy.
- They provide very little information on the extent of problematic polypharmacy and what interventions to address it are effective in the UK.
- Problematic polypharmacy in the UK is now an area requiring further research to help inform UK health policy.

2 | METHODS

2.1 | Overview

Given the wide range of commissioned topics and questions, and the two-month timeframe to present the findings to the DHSC, a rapid review of existing systematic reviews in problematic polypharmacy was undertaken. The study was undertaken in accordance with the current Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[7] The protocol for the rapid review is registered with PROSPERO (CRD42019141295).

2.2 | Searches

MEDLINE (via Ovid), Embase (via Ovid) and Cochrane Database of Systematic reviews (via Wiley) were searched to June 2019 to identify systematic reviews on problematic polypharmacy. The search was limited to systematic reviews, in English, published in the last 10 years and in people aged 65 years and over. The search did not look for evidence on specific activities/interventions given that none were pre-specified by the SLWG. A copying of the MEDLINE search strategy is presented in Appendix 1.

2.3 | Inclusion and exclusion criteria

Systematic reviews were included if they were full-text, peer-reviewed publications that evaluated any of the four topics (burden of problematic polypharmacy, interventions to reduce problematic polypharmacy, implementation activities to increase uptake of interventions to reduce

problematic polypharmacy, and efficient handover between primary and secondary) and associated research questions for this rapid review. The burden of problematic polypharmacy was defined as consequences on health (measured with any health outcome measures, but with specific attention to health-related quality of life and mortality), resource use or costs.

Problematic polypharmacy was defined in accordance with the definition provided by the King's Fund as "prescribing of multiple medications inappropriately, or where the intended benefit of the medication is not realised".[3] Where no systematic review using this definition was available for a specific research question, other systematic reviews were eligible for inclusion as long as their focus was on problematic polypharmacy.

Only systematic reviews that were awarded a "yes" on four of the AMSTAR-2 (A MeaSurement Tool to Assess systematic Reviews) quality checklist criteria[8] were included, as follows: the search strategies were comprehensive, data extraction was performed in duplicate, a satisfactory technique was used to assess study quality, and the included studies were described in adequate detail. We considered these criteria important in the context of the reproducibility of the review, the accuracy of the data it contains, interpretation of the quality of the evidence included and the transparency of the review findings.

There were no restrictions on country, except to inform the topic on burden of problematic polypharmacy (where reviews had to include UK studies), no restrictions in the location of care and no restrictions on outcomes.

2.4 | Study selection and data extraction

One reviewer screened the records to identify the included studies and undertook the data extraction and quality assessment. A second independent reviewer checked the extracted data (including the quality assessment) against the publications for accuracy. Data that were extracted included the review question, the patient population and/or setting, the number of included studies and the number conducted in the UK, interventions and comparators (where appropriate), outcomes and information to inform the AMSTAR-2 assessment for this rapid review. A copy of the extracted data from the included systematic reviews is presented in Appendix 2. As this was a rapid review, details of the included UK studies were extracted directly into Table 1 (Appendix 3).

2.4.1 | Quality assessment

We assessed the methodological quality of included systematic reviews using the AMSTAR-2 checklist.[8]

2.5 | Synthesis

A narrative evidence synthesis was undertaken. No meta-analysis was planned. A GRADE (Grading of Recommendations Assessment, Development and Evaluation) was not planned.

3 | RESULTS

3.1 | Study selection

The PRISMA flow diagram of the study selection process is presented in Figure 1. Following deduplication, 481 unique records were identified, 459 of which were excluded at the title/abstract screen. Twenty-two potentially relevant full-text articles were obtained, 12 of which were excluded. The table of the 12 articles excluded at the full-text stage, with reason for exclusion, is presented in Appendix 3. Of the 12 articles, five were excluded based on the quality assessment criteria for inclusion in this rapid review. Details of the quality assessment judgements for exclusion, along with the topic covered by the excluded reviews, are also presented in Appendix 3. Nine systematic reviews (across 10 publications) were included in this rapid review.[9,10,13,16,18,19,24,32,48,49]

3.2 | Overview of included studies

All of the included systematic reviews were international, with most including some UK studies. Table 1 summarises the systematic reviews by topic, including the number of included studies, the definition of polypharmacy for studies to be included, the number of included studies conducted in the UK and the key findings of each systematic review. Where UK studies were included in a systematic review, a brief summary of each UK study is also presented in Table 1. Studies were considered to be in the UK if they were set in England and/or Wales and/or Scotland and/or Northern Ireland (but not if the systematic review indicated the study as being in Ireland).

None of the included systematic reviews reported using the King's Fund definition of polypharmacy for included studies.[3] Six of the systematic reviews did not report any definition of polypharmacy for included studies.[13,16,18,19,24,32,48] Two systematic review defined polypharmacy as ≥four medications,[9,49] and one define polypharmacy as ≥five medications.[10]

3.3 | Burden of problematic polypharmacy: Findings

Three systematic reviews were on the topic of the burden of problematic polypharmacy.[18,24,32] Jokanovic et al[24] evaluated the prevalence of, and the factors associated with, polypharmacy in people living in long-term care facilities. The review included 44 studies, three of which were UK studies.[11,12,14] Leelakanok et al[32] undertook a systematic review and meta-analysis on the association between polypharmacy and mortality risk in various populations and settings. The review included 47 studies, two of which were in the UK.[38,39] Hill-Taylor et al[18] (previous review to the 2016 update[18]) evaluated the prevalence of potentially inappropriate prescribing (PIP) in older adults and the effectiveness of the application of the Screening Tool of Older Persons' potentially inappropriate prescriptions/Screening Tool to Alert doctors to the Right Treatment (STOPP/START). It included 13 studies, one of which was in the UK.[15]

TABLE 1 Summary of included systematic reviews and included UK studies

Study	Definition of polypharmacy for included studies	Total number of studies (UK)	Included UK studies	Key findings across all included studies
Topic: Burden of PP (six UK studies out of 104)				
Jokanovic et al[24]	Not defined	44 (3)	• Gadsby et al was a retrospective case notes review in 75 people with diabetes living in 11 long-term care facilities. They found that 45.3% of patients were on 4-7 medicines, 24.7% on 8-11 medicines and 4% on 13+ medicines[11] Honney et al was a cross-sectional study of 316 people living in a long-term care facility who had an emergency hospital admission. They found that 50.5% were on 4-7 medicines and 42.1% were on 9+ medicines[12] • Whitney et al was a prospective cohort study in 240 patients aged over 60 years and resident in 10 long-term care facilities. They found that 69% were on 7+ medicines[14]	• Studies varied on the definition of polypharmacy • Prevalence of polypharmacy varied by study • Polypharmacy more likely with greater number of comorbidities, recent hospital discharge and greater number of prescribers • Polypharmacy less likely with older age, cognitive impairment, impairment in activities of daily living and length of stay in long-term care facility
Leelakanok et al[32]	Not defined	47 (2)	• Richardson et al was a prospective cohort study in England and Wales comparing the outcomes of 1586 older people on ≥5 medicines with 10 837 people on <5 medicines over 18 years of follow-up. The risk ratio for all-cause mortality controlling for age and comorbidities was 1.30 (95% CI 1.19 to 1.42)[14] • Shah et al was a retrospective cohort study using routine healthcare records, comparing the outcomes of a community cohort of 354 306 patients on 0-2 medicines with those of an institutional cohort of 9772 patients on 6-10 medicines. The risk ratio for all-cause mortality, and adjusting for age, sex, comorbidities and other characteristics was 1.96 (95% CI 1.42 to 2.71)[15]	• Studies varied on the definition of polypharmacy • Polypharmacy is associated with higher mortality risk
Hill-Taylor et al[16]	Not defined	13 (1)	• Parsons et al conducted an observational cross-sectional study which applied the partial STOPP criteria to 119 people living with dementia in long-term care facilities whose mean age was 87 years. The mean number of medicines was 8, 41-46% had ≥1 PIMs[17]	• The prevalence of PIMs varied between 21% and 79% and the prevalence of PPO varied between 23% and 74% • Higher prevalence of PIMs and PPOs was associated with older age, female sex, polypharmacy and comorbidities The direct cost of PIP (PIM or PPO) was estimated in three studies at €263-€318 per patient per year (Northern Ireland and Republic of Ireland); no further details were provided in the systematic review
Topic: Interventions to reduce PP (27 UK studies out of 240)				
Clyne et al[8]	Not defined	12 (0)	• None in UK	• Organisational interventions reduce PIP (N = 4 out of 6 RCTs) • Evidence of the effectiveness of multidisciplinary teams was weak • Clinical decision support systems reduce new PIP but not existing PIP (N = 2 RCTs) • Multifaceted interventions reduce PIP (N = 3 out of 4 RCTs)

TABLE 1 (Continued)

Study	Definition of polypharmacy for included studies	Total number of studies (UK)	Included UK studies	Key findings across all included studies
Hill-Taylor et al[16,18]	Not defined	15 (1)	• Parsons et al conducted an observational cross-sectional study which applied the partial STOPP criteria to 119 people living with dementia in long-term care facilities whose mean age was 87 years. The mean number of medicines was 8, 41-46% had ≥1 PIMs[17]	• 2013 review: There were some challenges in applying the STOPP/START criteria (version not specified but likely version 1) • 2013 review: Six studies found the STOPP criteria more sensitive than Beers to detect PIP • 2016 review: Interventions increased the chances that PIMs were reduced (random effects; OR 2.98; 95% CI 1.30, 6.93; N = 4 RCTs; *I*-squared = 87.6%)
Johansson et al[19]	≥4 medications	25 (4)	• Lenaghan et al was an RCT comparing home-base medication reviews by a pharmacist with usual care in 134 community-dwelling older people over 6 months' follow-up.[20] The primary outcome was number of non-elective admissions (RR 0.92; 95% CI 0.50, 1.70); other outcomes included change in EQ-5D index scores (MD 0.09; 95% CI 0.19, 0.02), change in EQ-5D VAS (MD 4.8; 95% CI −12.5, 2.8) and number of items prescribed (MD −0.87; 95%CI −1.66, −0.08). • Pope et al was an RCT comparing specialist geriatric input and medication review compared with usual care (review as required by a medical officer) in 225 people in continuing-care wards over 6 months' follow-up.[21] The primary outcomes were number of drugs prescribed (statistical measures of effect not reported) and medication cost (net reduction in total medication cost = £20 per person) • Zermasky et al was an RCT comparing clinical medication review by a pharmacist with usual care in 661 older people living in care homes over 6 months.[22] The outcomes included number of repeat drugs per patient at follow-up (MD 0.98; 95% CI 0.92, 1.04), hospitalisations per patient (OR 0.75; 95% CI 0.52, 1.07), mortality (OR 0.89; 95% CI 0.56, 1.41), drug cost (MD −£0.70; 95% CI −£7.28, £5.71) and number of GP consultations (MD 1.03; 95% CI 0.93, 1.15) • Sturgess et al was an RCT comparing a structured pharmaceutical care programme with usual care in 191 community-dwelling older people over 18 months' follow-up.[23] The outcomes included health-related quality of life measured with SF-36, number of hospitalisations, prescribed drug use, compliance to medication, number of contacts with healthcare professionals and cost of healthcare per patient. Only the *P* value of the effect was reported, not the summary measure of effect	• No effect on all-cause mortality and low levels of statistical heterogeneity (random effects; OR 1.02; 95% CI 0.84 to 1.23; N = 25 studies; *I*-squared = 8%; OR 1.05; 95% CI 0.85, 1.29; N = 16 RCTs; *I*-squared = 12%) • Very low quality evidence on the effect of interventions on hospitalisation • Limited evidence on reduction of polypharmacy

(Continues)

TABLE 1 (Continued)

Study	Definition of polypharmacy for included studies	Total number of studies (UK)	Included UK studies	Key findings across all included studies
Kua et al[24]	Not defined	41 (8)	• Ballard et al examined the discontinuation of neuroleptics by doctors and pharmacists over 3 months in 100 people and over 12 months in 165 people[25,26] • Ballard et al examined medication review using dementia guidelines by doctors over 9 months in 277 people[27] • Fossey et al examined education training and support on alternatives to drugs for the management of agitated behaviour in dementia by pharmacists over 12 months in 359 people[28] Furniss et al examined medication reviews by doctors and pharmacists over 3 months in 330 people[29] Jordan et al examined adverse drug reaction profiling by nurses over 6 months in 43 people[30] • Patterson et al examined medication review using a review model by pharmacists over 12 months in 334 people[31] • Zermanky et al examined medication review by pharmacists over 6 months in 661 people[22]	• Deprescribing was associated with lower mortality risk, although the studies' results were highly heterogeneous • No evidence to suggest an effect of deprescribing on falls and hospitalisation risk • Evidence to suggest that deprescribing reduced PIMs
Page et al[32]	Not defined	115 (15)	• Five studies were RCTs: Hearing et al on the deprescription of atenolol,[33] Ballard et al on the deprescription of antipsychotics,[25,26,34] Curran et al on the deprescription of benzodiazepines,[35] Borrill et al on the deprescription of inhaled fluticasone and salmeterol,[36] Choudhury et al on the deprescription of inhaled corticosteroids[37] • Three nonrandomised comparative studies: Minett et al on the deprescription of donezepil,[38] Cunnington et al on the deprescription of dopamine agonists,[39] Jarad et al on the deprescription of inhaled corticosteroids[40] • Seven studies were before-and-after studies: Alsop et al and Fortherby et al were before-and-after studies on the deprescription of antihypertensives,[41,42] Jackson et al on the deprescription of nitrates,[43] Sambu et al on the deprescription of clopidogrel,[44] Esselinckx et al on the deprescription of prednisolone,[45] Fair et al[46] and Daly and Edwards on the deprescription of digoxin[47]	• No effect on mortality (OR 0.82, 95% CI 0.61, 1.11; N = 10 studies, n = 3151 people; *I*-squared = 23%). • Some evidence to suggest that deprescribing polypharmacy leads to a reduction in the number of medicines and to a reduction in the number of PIMs • No evidence was found to suggest an increased risk of adverse outcomes and some evidence was found on benefits
Rankin et al[48]	≥4 medications	32 (0)	None in UK	• Evidence synthesis focussed on pharmaceutical care + standard care *vs* standard care • Statistically significant effect on medication appropriateness (random effects; MD −4.76; 95% CI −9.20, −0.33; N = 5 studies, n = 517; *I*-squared = 95%); number of PIMS (random effects; SMD −0.22; 95% CI −0.38, −0.05; N = 7 studies; n = 1832; *I*-squared = 67%), proportion of patients with one or more PPOs random effects; RR 0.40, 95% CI 0.18, 0.85; N = 5 studies; n = 1310; *I*-squared = 90%)

TABLE 1 (Continued)

Study	Definition of polypharmacy for included studies	Total number of studies (UK)	Included UK studies	Key findings across all included studies
				• Non-significant effect on the proportion of patients with one or more PIMs (random effects; RR 0.79; 95% CI 0.61, 1.02; N = 11 studies, n = 3079; I-squared = 85%); no consistent effect on medication-related problems; no evidence of impact on quality of life or hospitalisations
Topic: Efficient handover between primary and secondary care (2 UK studies out of 25)				
Redmond et al[49]	≥5 medications	25 (2)	• Cadman et al was an RCT comparing a standardised operating procedure based on hospital guidelines to deliver medication reviews by trained MRP within 24 hours of admission and at point of transfer of care out of hospital against usual care in 200 people at hospital admission.[50] The outcomes included length of stay (MD –0.40; 95% CI –2.08, 1.29), unintentional discrepancies (not reported), hospital readmissions (RR 0.86; 95% CI 0.58, 1.28), mortality (RR 0.75; 95% CI 0.27, 2.08) and EQ-5D-3 L index scores (not reported) • Bolas et al was an RCT comparing a medicines reconciliation intervention with standard clinical care in 243 people after an emergency or unplanned admission to a hospital in Northern Ireland.[51] The primary outcome was unclear; other outcomes included Eadon scores, medicines discrepancies, emergency readmission rates and rates of reconciliation. No results were reported	• Medicine reconciliation interventions reduced the proportion of people with at least one medication discrepancy compared to standard care (random effects; RR 0.53; 95% CI 0.42, 0.67; N = 20 RCTs, n = 4,629; *I*-squared = 91%) Non-significant reductions in the number of discrepancies per person and the number of discrepancies per participant medication, with high levels of statistical heterogeneity • Limited effect on PADEs (RR 0.37. 95% CI 0.09, 1.57; N = 3 RCTs; n = 1253; *I*-squared = 84%) or on ADEs (RR 1.09, 95% CI 0.91 to 1.30; N = 4 RCTs; *I*-squared = 0%). • Conflicting evidence on healthcare utilisation: RR on composite measure of emergency department, rehospitalisation 0.78; 95% CI 0.50, 1.22; N = 4 RCTs; n = 1363; *I*-squared = 48%)

Abbreviations: ADEs, adverse drug events; CI, confidence interval; EQ-5D, standardised instrument for measuring generic health status (not an acronym); MD, mean difference; MRP, medication reconciliation pharmacist; OR, odds ratio; PADEs, preventable adverse drug events; PIM, potentially inappropriate medicine; PIP, potentially inappropriate prescribing; PP, problematic polypharmacy; PPO, potentially prescribing omission; RCT, randomised controlled trial; RR, relative risk; SF-36, 36-Item Short-From survey; SMD, standardised mean difference; STOPP, Screening Tool of Older People's potentially inappropriate Prescriptions.

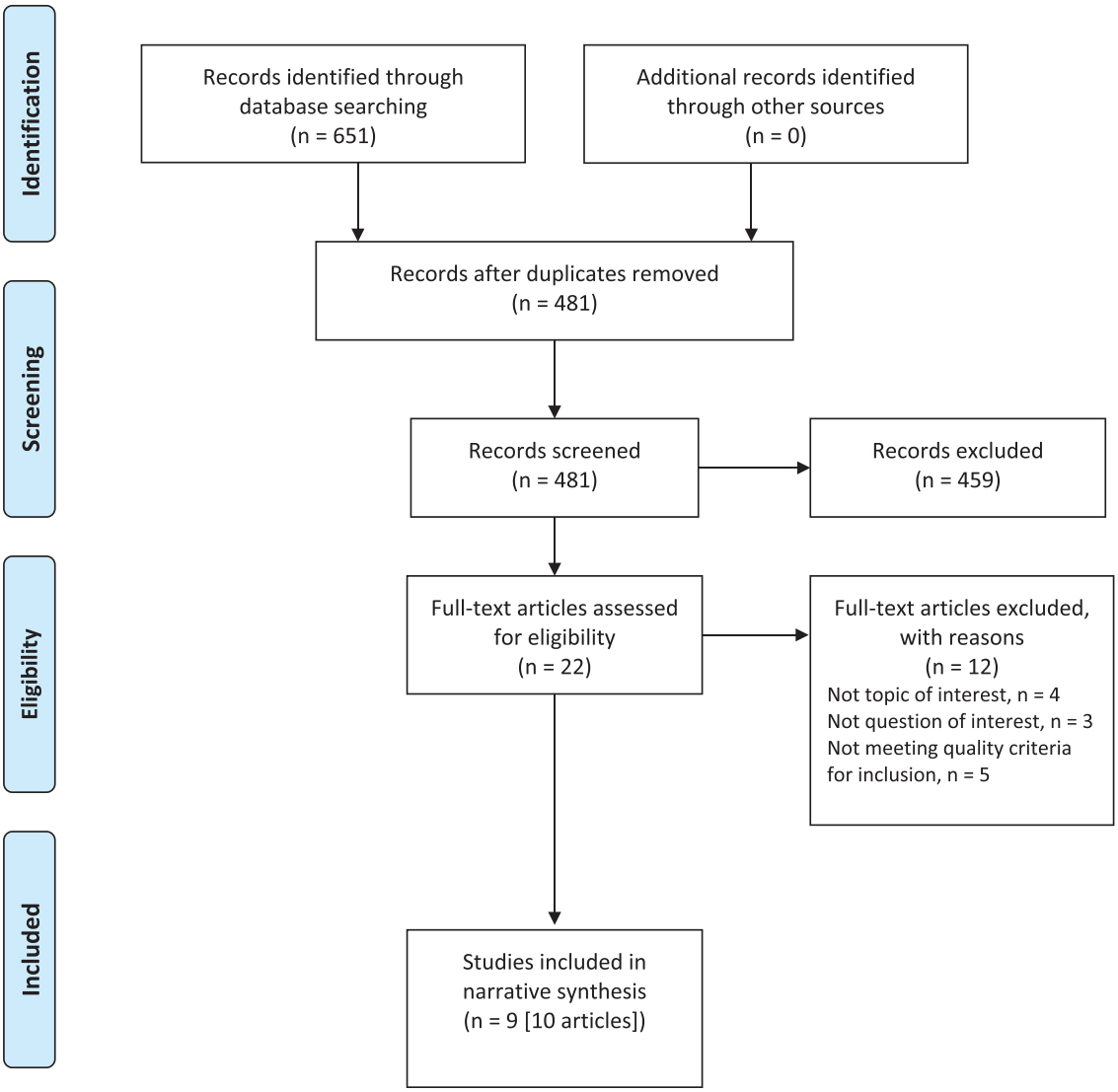

FIGURE 1 PRISMA 2009 flow diagram

Both Jokanovic et al[24] and Leelakanok et al[32] suggested that there is no consensus in the literature on the definition of polypharmacy. Jokanovic et al[18] found that the prevalence of polypharmacy in people residing in long-term care facilities was high. Leelakanok et al[32] found that polypharmacy is associated with greater risk of death, although this may not reflect a causal effect due to confounding in the meta-analysis. Hill-Taylor et al[18] found that the prevalence of PIPs varied and that higher prevalence was associated with older age, female sex, polypharmacy and comorbidities. The review found some evidence on direct costs of PIP outside of the UK (Table 1),[17,20,21] but not cost-effectiveness.

3.4 | Burden of problematic polypharmacy: Quality assessment

Table 2 presents the results from the AMSTAR-2 quality assessment. The AMSTAR-2 quality assessment indicated some limitations relating to lack of clarity on an a priori protocol,[24,32] sources of funding of the included studies[24,32] and details on the excluded studies.[24,32] There were also AMSTAR-2 quality limitations in the meta-analysis by Leelakanok et al,[32] in that estimates from different study designs, analytical approaches and quantities were pooled together. Hence, the results of their review should be interpreted as evidence of association, albeit uncertain, and not as evidence of a causal effect. Furthermore, the authors did not clearly define the inclusion criteria for studies, report on the study selection process or consider study quality in the meta-analysis.

3.5 | Interventions to reduce problematic polypharmacy: Findings

Six systematic reviews were on the topic of interventions to reduce problematic polypharmacy,[9,13,16,18,19,48,49] one of which was on the effectiveness of deprescribing guidelines to reduce problematic

TABLE 2 AMSTAR-2 quality assessment of the included systematic reviews

Study	Is there a clear research question and inclusion criteria for studies?	Were methods established prior the review in a protocol?	Were study designs for inclusion in the review reported?	Was there a comprehensive literature search strategy?	Was study selection undertaken in duplicate?	Was data extraction undertaken in duplicate?	Is there a list of full-text excluded studies with reasons?	Are the included studies described in adequate detail?
Clyne et al[8]	Yes	NR	Yes	Yes	Yes	Yes	No	Yes
Hill-Taylor et al[16,18]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Johansson et al[19]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Jokanovic et al[9]	Yes	NR	Yes	Yes	Yes	Yes	No	Yes
Kua et al[24]	Yes	NR	Yes	Yes	Yes	Yes	No	Yes
Leelakanok et al[13]	No	NR	No	Yes	No	Yes	No	Yes
Page et al[32]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Rankin et al[48] (Cochrane review)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Redmond et al[49] (Cochrane review)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Abbreviations: NA, not applicable; NR, not reported.

polypharmacy.[13] No systematic reviews were found that evaluated the effectiveness of using routine data to reduce problematic polypharmacy or the effectiveness of digital technologies to reduce problematic polypharmacy.

Clyne et al[16] evaluated the effectiveness of interventions to reduce PIP in community-dwelling older adults. The review included 12 studies, none of which were undertaken in the UK. Page et al[48] evaluated the safety, effectiveness and feasibility of deprescribing interventions on mortality and other health outcomes. The review included 115 studies, 15 of which were UK studies on deprescribing.[22,23,25–31,33–40] Hill-Taylor et al[19] evaluated the effectiveness of the STOPP/START criteria (likely to be version 1[41] from the dates of the included studies). The review included four studies (one of which was in also in Hill Taylor[18]), none of which were undertaken in the UK. Kua et al[13] evaluated the effectiveness of deprescribing on polypharmacy in people living in nursing homes. The review included 41 studies, eight of which were UK studies evaluating discontinuation,[25,26] medication review,[42–45] education training and support on alternatives,[46] and adverse drug reaction profiling.[47] Rankin et al[49] evaluated the effectiveness of interventions to improve the appropriate use of polypharmacy and reduce medication-related problems in older people. The review included 32 studies, none of which were undertaken in the UK.

All of these systematic reviews found that the interventions they evaluated were effective at reducing problematic polypharmacy.[13,16,19,48,49]

Hill-Taylor et al[18,19] also concluded that the STOPP/START criteria could be useful to help identify people at risk of potentially inappropriate prescribing, but concluded that more research is required on its feasibility and effectiveness.

Johansson et al[9] undertook a systematic review and meta-analysis of the effectiveness of interventions to reduce polypharmacy on mortality, hospitalisation and number of drugs in elderly patients and included 25 studies. The review included four UK studies on medication review[45,50,51] and pharmaceutical care programmes.[52] The review found no effect on all-cause mortality, as did Page et al[48] and, to some extent, Kua et al.[13] Both Johansson et al[9] and Clyne et al[16] also found that there was no clear evidence of an effect on clinically relevant patient outcomes.

From a safety perspective, Page et al[48] found no evidence to suggest that deprescribing increases the risk of adverse outcomes. From the reviews by Page et al,[48] Kua et al[13] and Rankin et al,[49] the evidence was mixed on the effect on disease-specific outcomes, quality of life and hospitalisations.

3.6 | Interventions to reduce problematic polypharmacy: Quality assessment

The AMSTAR-2 quality assessment indicated some limitations relating to lack of clarity on an a priori protocol,[13] sources of funding of the included studies[13,16,49] and details on the excluded studies.[13,16,18,19]

TABLE 2 Continued

Study	Is there an appropriate quality assessment of studies?	Are the sources of funding for includes studies reported?	If there is a meta-analysis, are the methods appropriate?	If there is a meta-analysis, has study quality been considered in the analysis?	Is study quality used to interpret results and discussion?	Is there explanation for, and discussion of, observed heterogeneity?	If there is a meta-analysis, has publication bias been assessed?	Are of conflicts of interest, and funding for the review reported?
Clyne et al[8]	Yes	No	N/A	N/A	Yes	Yes	N/A	Yes
Hill-Taylor et al[16,18]	Yes	Yes	Yes	No	Yes	Yes	No	Yes
Johansson et al[19]	Yes	Yes	Yes	No	Yes	Yes	No	Yes
Jokanovic et al[9]	Yes	No	N/A	N/A	Yes	Yes	N/A	Yes
Kua et al[24]	Yes	No	No	No	Yes	Yes	Yes	Yes
Leelakanok et al[13]	Yes	No	No	Yes	Yes	Yes	Yes	Yes
Page et al[32]	Yes	Yes	Yes	No	Yes	Yes	No	Yes
Rankin et al[48] (Cochrane review)	Yes	No	Yes	No	Yes	Yes	Yes	Yes
Redmond et al[49] (Cochrane review)	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes

Abbreviations: NA, not applicable; NR, not reported.

There were also AMSTAR-2 quality limitations in the meta-analysis by Kua et al[13] given the choice of fixed-effects (rather the random-effects) in the presence of statistical heterogeneity. None of the five reviews presenting a meta-analysis considered study quality in the analysis.[13,18,19,48,49]

3.7 | Implementation activities to improve uptake of interventions to reduce problematic polypharmacy

No systematic reviews were found on this topic.

3.8 | Efficient handover between primary and secondary care to reduce problematic polypharmacy: Findings

One of the included systematic reviews was on the topic of efficient handover between primary and secondary care to reduce problematic polypharmacy.[10]

Redmond et al evaluated the effectiveness of medicines reconciliation on medication discrepancies, patient-related outcomes and healthcare utilisation during care transitions. The review included 25 studies, two of which were undertaken in the UK. One UK study evaluated a standardised operating procedure based on hospital guidelines to deliver medication[53] and the other evaluated a medicines reconciliation intervention.[54] The review found that the interventions implemented in the included studies reduced medication discrepancies at care transitions, although the evidence was deemed to have very low certainty. There was little or no effect on adverse drug events, preventable adverse drug events or health care utilisation, although these findings are also uncertain due to the methodological quality of the primary studies observed by the review authors. The review authors also identified the possibility of a publication bias in the review.

3.9 | Efficient handover between primary and secondary care to reduce problematic polypharmacy: Quality assessment

The AMSTAR-2 quality assessment (Table 2) indicated some limitations relating to sources of funding of the included studies and consideration of study quality in the meta-analysis.

4 | DISCUSSION

4.1 | Summary of findings

This rapid review summarised the evidence on problematic polypharmacy related to burden, interventions and handover between primary and secondary care. The rapid review included nine

systematic reviews: three on the burden of problematic polypharmacy,[18,24,32] six on interventions to reduce problematic polypharmacy,[9,13,16,18,19,48,49] and one on efficient handover between primary and secondary care to reduce problematic polypharmacy.[10] All reviews were international, with most including some UK studies. No systematic reviews were found on implementation activities to increase uptake of interventions to reduce problematic polypharmacy.

For the topic of the burden of problematic polypharmacy, the evidence from one review suggests that the prevalence of polypharmacy in people residing in long-term care facilities is high, although it varies widely by country, setting and definition of how many medicines constitute polypharmacy.[24] The UK studies in the review found that the majority of people in long-term care facilities were on multiple medicines.[11,12,14] The evidence on the association between polypharmacy and greater mortality risk was mostly international. However, due to confounding bias in the evidence, any association is unlikely to reflect a causal effect. From one systematic review,[18] three studies were found on the costs due to problematic polypharmacy, but none was in the UK.[17,20,21] For these reasons, the prevalence of polypharmacy and problematic polypharmacy, and the costs and health consequences due to problematic polypharmacy in the UK remain unclear.

For the topic of interventions to reduce problematic polypharmacy, the evidence suggests that the interventions can reduce problematic polypharmacy, although reductions in the number of medicines are more uncertain. Deprescribing and other interventions to reduce problematic polypharmacy appear to have no effect on all-cause mortality, but there is no clear evidence of an effect on other clinically relevant outcomes, quality of life and hospitalisations.

For the topic of efficient handover between primary and secondary care to reduce problematic polypharmacy, there is some evidence that medicine reconciliation activities reduce medication discrepancies at care transitions, although the quality of the evidence is low.

4.2 | Summary of methodological quality

Across all topics and reviews, the AMSTAR-2 quality assessment was variable, with limitations observed relating to lack of clarity on an a priori protocol, sources of funding of the included studies, details of excluded studies and consideration of study quality in the meta-analysis (where undertaken).

For one systematic review on the topic of the burden of problematic polypharmacy[32] and one on the topic of interventions to reduce problematic polypharmacy,[13] there were also some concerns with the AMSTAR-2 domain regarding the methods for the meta-analysis, indicating that the results from these reviews should be interpreted with caution.

4.3 | Areas for future research

For the topic of the burden of problematic polypharmacy, as the existing systematic reviews suggest that there is no consensus in the literature on the definition of polypharmacy, the prevalence of polypharmacy in people residing in long-term care facilities is high and there may be an association between polypharmacy and mortality risk in various populations and settings, further research is warranted:

- To estimate the prevalence of polypharmacy and the prevalence of problematic polypharmacy in all UK settings, according to a definition that represents the current expert consensus.
- To identify the factors that predict problematic polypharmacy in the UK with the aim of routinely identifying people at risk of problematic polypharmacy and who should be prioritised for interventions to reduce problematic polypharmacy.
- To estimate the causal effect of problematic polypharmacy on costs and on health outcomes; in other words, what would have been the costs and health outcomes of a group of people exposed to problematic polypharmacy had they not been exposed to problematic polypharmacy?

This could be undertaken by further systematic review work, including an update of the existing reviews to identify further UK studies, along with further primary investigation studies undertaken in the UK. Further work could also involve using routinely collected electronic health records to estimate prevalence of problematic polypharmacy, identify predictive factors and infer causal effects.

For the topic of interventions to reduce problematic polypharmacy, given that the existing systematic reviews have found that, although the interventions were effective at reducing problematic polypharmacy there is no clear evidence of an effect on clinically relevant patient outcomes, the areas for future research are:

- The comparative effectiveness of each intervention to reduce problematic polypharmacy, considering the quality of the primary studies and their generalisability to the UK and considering the role of routine data and digital technologies. Answering this research question could involve an update of the existing reviews.
- To estimate the resources and costs required to implement and run the various interventions.
- To estimate the cost-effectiveness of the interventions, with cost-effectiveness modelling of the long-term costs and health outcomes of current practice with or without interventions, given the prevalence of problematic polypharmacy, the consequences of problematic polypharmacy on costs and health outcomes, and the effectiveness of interventions in reducing problematic polypharmacy.

Given the lack of systematic review evidence on implementation activities to increase uptake of interventions to reduce problematic polypharmacy, future research (both systematic review and primary research) could explore the following areas:

- To understand the extent to which interventions to reduce problematic polypharmacy are used in the UK and, if uptake is suboptimal, to identify the barriers to uptake and the implementation activities that could address these.

- To review the literature and conduct evidence synthesis to estimate the comparative effectiveness of the relevant implementation activities in changing uptake, considering the quality of the primary studies, their design (eg, pragmatic trials) and their generalisability to the UK. Future reviews should prespecify the implementation activities on which evidence is sought on (eg, electronic decision support tools, tools for shared decision-making, etc)
- To conduct cost-effectiveness modelling of the value of implementation given the current uptake, the effectiveness of implementation activities, the cost-effectiveness of interventions to reduce problematic polypharmacy and the prevalence of problematic polypharmacy.

For the topic of efficient handover between primary and secondary care to reduce problematic polypharmacy, an update of the single systematic review of medicines reconciliation could be undertaken to identify further UK studies on this topic and to inform further primary research to consider, in addition to effectiveness, effect on adverse drug events, preventable adverse drug events, cost and healthcare utilisation, alongside consideration of the generalisability of the studies and feasibility of interventions to the UK setting. Further systematic reviews of other interventions for efficient handover between primary and secondary care to reduce problematic polypharmacy could also be undertaken.

4.4 | Strengths and limitations

Given the time and resource constraints, this rapid review does have some limitations. Due to single reviewer study selection, it is possible that eligible systematic reviews may have been missed at the study selection stage. The systematic review searches were highly specific, which may have also led to some relevant systematic reviews being missed. We adopted an abbreviated rapid review method in selecting and searching fewer, but relevant databases. The impact of searching beyond three databases was not investigated. Also, the search date restriction may have missed some key primary publications on medication reconciliation and problematic polypharmacy, although many of the reviews included studies published since the year 2000 and before.

Our rapid review methods, in which we abbreviated certain methodological aspects of the systematic review process, offered a pragmatic alternative to a systematic review, given the wide range of commissioned topics and questions, and the two-month timeframe to present the findings to the DHSC. Time permitting, a systematic review applying Heath Technology Assessment methods would have been considered. However, the rapid review approach allowed us to summarise the literature on the topics of interest and identify the areas where more research is required.

The systematic reviews included in this rapid review were not solely UK focused. As such, we included systematic reviews using any definition of polypharmacy, where the King's Fund definition was not used for selecting included studies. Definitions of polypharmacy used by reviews were often not reported or varied in the number of medications. Due to the time constraints of this commissioned rapid review, we were unable to extract the polypharmacy definitions of the included UK studies.

The systematic reviews included in the rapid review were published between 2013 and 2019, with searches undertaken some months prior to publication. As such, more recent evidence on the topics for this rapid review will not have been captured, and we were unable to supplement our rapid review with updated searches to identify newer evidence.

5 | CONCLUSIONS

This rapid review has summarised the evidence from existing systematic reviews on the burden of polypharmacy, interventions to reduce it and efficient handover between primary and secondary care to reduce it. No systematic reviews were found that evaluated the effectiveness of using routine data to reduce problematic polypharmacy, the effectiveness of digital technologies to reduce problematic polypharmacy or implementation activities to improve uptake of interventions. Most reviews included some UK studies.

The conclusions from this rapid review are that across existing systematic reviews there is no consensus in the primary evidence base on the definition of polypharmacy, the prevalence of polypharmacy in people residing in long-term care facilities is high and associated with greater mortality risk (although the link is unlikely to be causal), interventions to reduce problematic polypharmacy are effective but there is no evidence on clinically relevant patient outcomes, and there is some evidence that medicine reconciliation activities reduce medication discrepancies at care transitions, although the evidence has very low certainty.

In the UK, the prevalence of polypharmacy has increased over time. Problematic polypharmacy is a key area of interest for UK health policy. The systematic reviews included here provide very little reliable information on the extent of problematic polypharmacy in the UK, what interventions to address it are effective and the cost-effectiveness of interventions in the UK setting. There are also methodological issues with the existing systematic reviews, alongside the age of the existing systematic review searches. Therefore, a number of research questions are proposed to address the evidence gaps and to help directly inform UK policy on the topic.

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COMPETING INTERESTS

There are no competing interests to declare.

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APPENDIX 1

Pragmatic Medline search strategy

#	Searches
1	Polypharmacy/
2	Polypharma*.Ti,ab.
3	Polytherap*.Ti,ab.
4	((multi-drug* or multidrug*) adj2 (prescrib* or prescription* or therap* or treatment*)).Ti,ab.
5	Inappropriate prescribing/
6	Potentially inappropriate medication list/
7	((inappropriat* or unnecessary or multipl*) adj2 (medicine* or medicat* or prescrib* or prescription* or drug*)).Ti,ab.
8	((over adj1 (prescrib* or prescript*)) or (over-prescrib* or overprescrib*)).Ti,ab.
9	Deprescriptions/
10	(deprescrib* or deprescript*).Ti,ab.
11	Or/1-10
12	MEDLINE.Tw.
13	Systematic review.tw.
14	Meta analysis.pt.
15	12 or 13 or 14
16	11 and 15
17	Limit 16 to elderly
18	Limit 17 to (English language and yr = “2009 -current”)

APPENDIX 2: EXTRACTED DATA FROM THE INCLUDED SYSTEMATIC REVIEWS

Data extraction of the methods of the included systematic reviews

Study	Objectives	Patient population	Interventions comparators	Outcomes
Jokanovic et al [12]	To investigate the prevalence and the factors associated with polypharmacy in long-term care facilities	People resident in long-term care facilities	Exposure to polypharmacy Polypharmacy clearly defined	Prevalence of polypharmacy
Leelakanok et al [14]	To summarise the literature and conduct a meta-analysis of the association between polypharmacy and mortality risk	Adults (studies in children were excluded)	Exposure: Polypharmacy as multiple medication use, with explicit number of medications that were considered as polypharmacy	Outcomes: Death, reported in a way that can be used to calculate risk ratios (OR, RR, HR)
Clyne et al [8]	To review and determine the effectiveness of interventions to reduce PIP in community-dwelling older adults	Included: Community-dwelling older adults (aged ≥65 or had an average age of ≥65) Excluded studies in which more than 20% of the subject population was described as institutionalised (eg, nursing homes, residential care homes or geriatric inpatients) Studies that focused on the reduction of inappropriate prescribing in one drug class only were also excluded	Intervention: An intervention intended to improve PIP in primary care, including but not restricted to organisational, professional, financial, regulatory or multifaceted interventions Comparator: Usual care or alternate intervention	Primary outcome: Change in PIP, measured using specified implicit or explicit tools (eg, beers, STOPP, MAI)
Hill-Taylor et al [9, 10]	To update the 2013 systematic review using new evidence from RCTs that assess the effectiveness of STOPP/START criteria on prescribing quality and clinical, humanistic and economic outcomes in adults aged 65 years and older	Adults aged 65 years and older	Intervention: STOPP/START criteria Comparator: Not reported	2013: Indicators of the clinical and humanistic impact of the use of STOPP/START criteria on the patient and healthcare system (ADEs, physician visits, emergency department visits, hospitalization and quality of life) 2016: Studies that measured robust indicators of the clinical, humanistic and economic impact of the application of the criteria Outcome for the meta-analysis was odds ratio of

Study	Objectives	Patient population	Interventions comparators	Outcomes
				patients having at least one PIM after intervention
Johansson et al [11]	To review strategies to assess and reduce inappropriate polypharmacy in elderly patients on relevant clinical outcome measures such as mortality and hospitalisation	Included: Older patients age ≥ 65 years (or 80% of study population aged ≥65 years) with polypharmacy, 4 or more prescribed or nonprescribed drugs (or 80% of study population taking ≥4 drugs) Excluded: Approaches investigating under prescription (eg, "start interventions") and interventions focusing on people receiving short-term polypharmacy (eg, terminally ill or receiving cancer chemotherapy)	Interventions: Electronic strategies to reduce polypharmacy (clinical decision support, computerized physician order entry, others) Comparators: No intervention or usual care (other comparable intervention)	Primary: Mortality, hospitalisation, change in n drugs Secondary: Morbidity, QoL, mental and physical function, ADEs, medication error/ inappropriate, focus of care, user/patient satisfaction, adherence, resource utilisation, and costs
Kua et al [13]	To review the effects of deprescribing studies on clinical outcomes that have been performed among older residents in nursing homes	Included: Nursing home residents ≥60 years of age Excluded: Terminal or palliative care-requiring nursing home residents	Intervention: Drug discontinuation defined as either medication discontinuation, substitution or reduction	Any reported health outcomes (including falls, inappropriate medications, all-cause mortality, and hospitalisation rates)
Page et al [15]	To review the safety, effectiveness and feasibility of deprescribing interventions on mortality and health outcomes	Included: Patients aged 65+ years on 1+ regular medicines Excluded: Patients at the end of life Setting: Any	Interventions: Deprescribing by a healthcare professional of medicines available in 2015 (excludes medicines withdrawn from the market) Comparators: Usual care (ie, continuation of medication) Studies were pooled as "polypharmacy" where the stated aim or effect of the intervention was to reduce medications across three or more medications or classes	Primary outcome: Mortality Secondary outcomes: Reported adverse drug withdrawal events, clinically relevant physical health, cognitive function, psychological health, quality of life using any standardised tool
Rankin et al [16]	To review the effectiveness of interventions to improve the appropriate use of polypharmacy and reducing medication-	Included: People aged 65 years and older, who had more than one long-term medical condition and were receiving	All types of interventions aimed at improving appropriate polypharmacy in any setting (such as pharmaceutical care)	Validated measures of inappropriate prescribing such as beers criteria, MAI, STOPP/START criteria, or assessing Care of

(Continues)

Study	Objectives	Patient population	Interventions comparators	Outcomes
	related problems in older people	polypharmacy (classified as four or more medicines Excluded: Studies in which the intervention focused on people with a single long-term medical condition or who were receiving short-term polypharmacy	compared with usual care (as defined by the study)	Vulnerable Elderly (ACOVE) that assessed primary outcomes (medication appropriateness, potentially inappropriate medications, potential prescribing omissions, hospital admissions) and secondary outcomes (medication-related problems, eg, AEs, adherence, quality of life)
Redmond et al [17]	To review the effectiveness of interventions fulfilling the Institute for Healthcare Improvement definition of medication reconciliation aimed at all patients experiencing a transition of care	Included: Patients experiencing a transition of care Care transitions referred to changes in the level, location or providers of care as patients moved within the healthcare system Excluded: Trials investigating interventions to improve the quality of prescribing during care transitions, with no medication reconciliation focus	Studies where the intervention was broadly compliant with the process of medication reconciliation as outlined by the Institute for Healthcare Improvement The intervention must have been applied as patients transitioned from different levels or locations of care (or both)	Primary: Medication discrepancies Secondary: Participant-related and process outcomes, healthcare utilisation, additional outcomes (including AEs)

[1] AE, ; ADE, ; ARR, absolute risk reductions; B&A, ; CI, ; HC, ; JBI, ; MAI, ; PIM, ; QA, ; QoL, ; QUIPS, ; RCT, ;RoB, RR, STOPP/START,Data extraction of the results of the included systematic reviews (number of studies, study design, population, setting, interventions/exposure and risk of bias)Data extraction on the results of the systematic reviews (outcomes)Data extraction on the conclusions of the included systematic reviews

Study	Types of studies	Study selection	Data extraction	Quality assessment	Data synthesis and analysis
Jokanovic et al [12]	Not defined	One investigator s creened the abstracts Two investigators assessed full text independently, and disagreements resolved by third investigator	Two investigators extracted the data independently using a standardised data extraction tool	Tool adapted from JBI critical appraisal checklist for descriptive/case series Two investigators did the QA independently, and disagreements resolved by a third investigator	Narrative synthesis
Leelakanok et al [14]	Not review articles; not case reports or case series	One researcher screened titles and abstracts Abstracts reviewed by two authors independently	Standardised data extraction form Two researchers did the data extraction independently	Two researchers did the QA independently and disagreements resolved by consulting two other researchers and by consensus	Random effects models with inverse variance weighting; *I*-squared < 30% was considered as negligible heterogeneity

Study	Types of studies	Study selection	Data extraction	Quality assessment	Data synthesis and analysis
			In case of disagreements, two other researchers were consulted and disagreements were resolved by consensus	Used the Newcastle-Ottawa quality assessment scale (scores 1-9) Studies scoring 1-3 were considered low quality, 4-6 medium quality, 7-9 high quality	Stratification by type of risk ratio, number of medications, HC setting (community, hospital, institutional) and study quality Number of polypharmacy classifications categorised in three groups: studies defining polypharmacy as a discrete variable, studies dichotomising polypharmacy using thresholds of <10 drugs (polypharmacy), studies dichotomising polypharmacy using thresholds of 10+ drugs (excessive polypharmacy) Funnel plot for publication bias
Clyne et al [8]	Randomised controlled trials and cluster randomised controlled trials only	Three reviewers independently assessed studies for eligibility	Three reviewers independently extracted data	Methodological quality was assessed using the Cochrane Collaboration's risk of bias tool	The studies identified were too heterogeneous in terms of their outcome measures and intervention types to conduct a meta-analysis, so a narrative summary was performed Where appropriate, crude odds ratios and ARRs were calculated
Hill-Taylor et al [9, 10]	2013: Randomised trials and non-randomised study designs investigating the impact and application of the STOPP/START 2016: RCTs involving the prospective application of the STOPP and/or START criteria	2013: Study selection was performed independently in an unblinded standardised manner by two authors (DOS and BHT) 2016: Two review authors independently appraised the search results for eligibility (KW and BHT).	2013: Two authors independently performed the data extraction (DOS and BHT) One author checked extracted data for agreement (BHT) 2016: Both review authors independently abstracted	2013: Methodological quality was assessed using the Cochrane Collaboration's risk of bias tool and modified quality assessment scale initially designed for studies of	2013: Heterogeneity of study populations, interventions and study design precluded meta-analysis Descriptive analysis was performed 2016: A random-effects meta-analysis to synthesise evidence on

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Study	Types of studies	Study selection	Data extraction	Quality assessment	Data synthesis and analysis
			data from selected studies (KW and BHT).	prognostic factors (QUIPS) 2016: Cochrane RoB	the effectiveness of the STOPP criteria on reducing the PIM rate in patients due to anticipated clinical heterogeneity A narrative synthesis was performed for all other outcomes
Johansson et al [11]	All types of controlled studies (randomised controlled trials, cluster randomised controlled trials, nonrandomised controlled trials, cohort studies and case control studies)	Two reviewers independently screened each title and abstract for eligibility	One author extracted the data and a second author independently extracted the data and then checked the completeness	Risk of bias was assessed according to the Cochrane collaboration handbook The quality of the evidence was assessed using the grading of recommendations, assessment, development and evaluation (GRADE) methodology Four of 25 included studies where not RCTs, but were quality assessed using RoB	Random effects meta-analysis and sensitivity/subgroups on methodological quality and length of follow-up
Kua et al [13]	Randomised controlled trials	Not reported	Two investigators extracted the data and reviewed each entry for accuracies	Two investigators undertook quality assessment	Fixed and random effects (where Cochran Q test *P* value <0.05) meta-analysis and subgroups by intervention type, medication type, intervention provider and study location
Page et al [15]	Any comparative design: RCTs, quasi-randomised controlled studies, nonrandomised controlled studies, cohort studies, case-control, 2+ single-arm studies, B&A studies; in English	Two researchers independently for all titles, abstracts and full-text studies Disagreements resolved by consensus	Standardised data extraction form Extraction by one researcher and verified by a second researcher Authors of original studies contacted for missing or unclear information	Assessment of risk of bias done with Cochrane risk of bias tool for RCTs and a modified tool for non-RCTs, done by two researchers independently	Studies meta-analysed where possible Studies pooled as "polypharmacy" where 3+ medication classes were targeted for deprescribing Heterogeneity assessed with *I*-squared (*I*-squared ≤50%) or *P* > 0.1 Subgroup analyses when more than 10 studies were found for the same target medication; based

Study	Types of studies	Study selection	Data extraction	Quality assessment	Data synthesis and analysis
					on age (under or above 80 years of age), cognitive function (with or without dementia), and intervention method (patient-specific interventions or educational programmes) Patient-specific interventions are those when the investigators identified target medications to deprescribe and implemented the process/asked prescribed to implement it
Rankin et al [16]	Randomised controlled trials, cluster-randomised trials, nonrandomised trials, controlled before-after studies and interrupted time series	Three reviewers (AR, CAC and JC) independently screened titles and abstracts	Three reviewers (AR, CAC and JC) independently extracted data	Risk of bias was assessed according to the Cochrane collaboration handbook The quality of the evidence was assessed using the grading of recommendations, assessment, development and evaluation (GRADE) methodology	In the presence of statistical heterogeneity (greater than 50%, as estimated by the I2 statistic), applied a random-effects model for meta-analysis For pooling, only groups of studies of the same design (randomised trials and nonrandomised trials) When it was not possible to combine outcome data because of differences in reporting or substantive heterogeneity, a narrative summary was reported
Redmond et al [17]	Randomised controlled trials	Two review authors independently screened titles and abstracts	Two review authors independently undertook data extraction	Modified Cochrane RoB The quality of the evidence was assessed using the grading of recommendations, assessment, development and	Pooled estimates (RRs with 95% CIs) of the evaluated outcome measures were calculated by the generic inverse variance method

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Study	Types of studies	Study selection	Data extraction	Quality assessment	Data synthesis and analysis
				evaluation (GRADE) methodology	Where it was not possible to synthesise the data from the included studies, a narrative synthesis of the results, grouping together studies that used similar interventions and provided a comparison of different approaches, was undertaken

[a]AE, ; ADE, ; ARR, absolute risk reductions; B&A, ; CI, ; HC, ; JBI, ; MAI, ; PIM, ; QA, ; QoL, ; QUIPS, ; RCT, ;RoB, RR, STOPP/START,
[b]Data extraction of the results of the included systematic reviews (number of studies, study design, population, setting, interventions/exposure and risk of bias)
[c]Data extraction on the results of the systematic reviews (outcomes)
[d]Data extraction on the conclusions of the included systematic reviews

Data extraction of the results of the included systematic reviews (number of studies, study design, population, setting, interventions/exposure and risk of bias)

Study	Number of studies	Study design	Population	Setting	Interventions/exposure	Risk of bias
Jokanovic et al [12]	N = 153 records after duplicates removed; 44 studies included in the review (total number of study participants not reported)	Not summarised	Residents in LTCFs with mean age ranged 61.7-86.0 years Four studies focused on residents with lengths of stay longer than 1 or 3 months, four studies focused on residents with cognitive impairment, two studies on residents presented to hospital, in residents with diabetes, one in residents who had experienced a fall, one in veteran	LTCFs	Exposure was polypharmacy Medication use was ascertained from medication charts or medical records (n = 24), drug registers or databases (n = 6), administrative or minimum data sets (n = 5), resident interviews (n = 1) and pharmacist-conducted medication reviews (n = 1) Polypharmacy defined as 5+ medicines (n = 11), 9+ medicines (n = 13), 10+ medicines (n = 11)	All studies reported clearly defined inclusion criteria, 42 (95%) studies used objective criteria to assess outcomes, 20 (45%) studies aimed to have participants who were representative of all residents in the particular LTCF, 37 (84%) studies did not identify and control for confounding factors using multivariate analyses

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Study	Number of studies	Study design	Population	Setting	Interventions/exposure	Risk of bias
					Twenty-four studies included the use of all medications taken regularly and as needed to assess polypharmacy, six studies included only regular medication, 14 studies included only prescribed medication, 10 studies excluded specific medicines from the polypharmacy assessment, 11 studies reported the period of time during which exposure was assessed	
Leelakanok et al [14]	N = 3892 studies after duplicates removed, 47 studies data extracted and meta-analysed	Of the 47 studies, 26 prospective cohort, 11 retrospective cohort, five case control, four clinical trials, one cross-sectional study	36/47 studies were in people with mean age 65 + years, eight in people with mean age <65 years, one study did not provide the age	Not discussed	Definition of polypharmacy varied: 11 studies measured polypharmacy as a discrete number of medications, 12 as 1-4 medicines, 15 as 5+, 9 as 6-9, 11 as 10+. The methods to determine the number of medicines were not discussed in the review	According to Newcastle-Ottawa quality assessment scale, no studies were low quality, 19 were medium quality and 28 were high quality Funnel plot indicates some publication bias against negative and/or smaller studies
Clyne et al [8]	N = 749 records after duplicates removed, 12 studies included in the review	12 RCTs, with 156,529 participants PIP was measured using implicit criteria in four studies and explicit criteria in eight studies; the MAI was the only implicit measure Of the eight studies using explicit criteria, one used the beers criteria 1997 iteration, one the 2003 iteration, one used the McLeod crtieria and five used combinations of existing criteria or study-specific criteria	Across the 12 RCTs the mean age of participants ranged from 65 to 81 Baseline PIP prevalence ranged between 18% and 100%	In the community	Six RCTs were on organisational interventions (four on pharmacist interventions and two on multidisciplinary team approaches), two RCTs were on professional interventions (targeting prescribers directly) and four RCTs were on multifaceted interventions (combining two or more techniques)	Detection, attrition and reporting bias were low in most studies Randomization, allocation concealment and blinding were less reliably implemented or reported Protection against contamination was unclear in three cluster RCTs All cluster RCTs accounted for clustering

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Study	Number of studies	Study design	Population	Setting	Interventions/exposure	Risk of bias
Hill-Taylor et al [9, 10]	2013: N = 77 records after duplicates removed, 13 studies included in the review 2016: N = 230 records after duplicates removed, four studies included in the review	2013: 13 studies: a single randomised controlled trial and 12 observational studies This review includes the application of STOPP/START to the health records of approximately 344 957 adults 2016: Four RCTs with 1935 participants	2013: The mean age of participants ranged from 74. 9 to 86.9 years The majority of participants were female (from 53% to 80%) The majority of participants were from the Northern Ireland and the Republic of Ireland Prevalence of PIP between 21.4% and 79% although affected by heterogeneity in sample population and study design 2016: Participants in all four studies were at least 65 years of age, although one study restricted participants to those aged 75 years and older The majority of participants were female (from 53% to 73%) Healthcare systems from four nations were represented (Republic of Ireland, Belgium, Spain and Israel) Baseline PIM between 32.4% and 66.8%	2013: The majority of participants in the included studies were community dwelling 2016: Two RCTs following discharge from the acute care, two RCTs in LTCFs	2013: Five studies, including the RCT, applied the full STOPP and START criteria to participant's medication profiles, three studies applied the STOPP criteria, and one study applied the START criteria Seven of the observational studies compared STOPP/START with other explicit criteria 2016: Three RCTs used the criteria to assess prescribing quality, one1 RCT conducted in Ireland used the full STOPP and START criteria as a screening tool	2013: Study quality varied. Seven studies adequately controlled for bias related to the study participation, outcome, application of STOPP/START and confounding measurement domains. Three were considered at a low risk of bias due to methods of data and five at low risk of bias due to approach for application of the STOPP/START tool. One study was found to have a high risk of bias with regard to the application of the screening tool. Five studies were considered at moderate or high risk of bias in the statistical analysis and data presentation domains 2016: Two RCTs were at a low risk of bias in all key domains, but concern existed regarding the risk of bias in the other two RCTs
Johansson et al [11]	N = 19 052 records after duplicates removed, 25 studies included in the review (17 RCTs, four cluster RCTs, four nonrandomised controlled)	Seventeen RCTs, four cluster RCTs, four nonrandomised controlled studies; range 79-2454 per study	The mean age of study participants ranged from 69.7 to 87.7 years and the percentage of male participants ranged from 20% to 100%	Thirteen studies in general practitioner surgeries, two studies in primary care centres/general practitioner outpatient clinic, one in an internal medical clinic, one in a hospital, one in a chronic care geriatric facility, one in a residential hospital with continuous care wards, five in nursing	Thirteen studies were pharmacist-led interventions, four studies were physician-led the interventions and eight studies were multidisciplinary team-led interventions	The main limitations contributing to risk of bias were related to the design (eg, inadequate randomisation, intent-to-treat analysis, sample size and power calculation) or execution of the studies All studies were unclear on blinding of participants and personnel

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Study	Number of studies	Study design	Population	Setting	Interventions/exposure	Risk of bias
				homes and one in an assisted living facility		
Kua et al [13]	N = 1171 records after duplicates removed, 41 RCTs included in the review	Forty-one RCTs enrolling 18 408 residents	Thirty-four studies mean age between 80 and 90 years, and 69.4% female Fifteen studies specifically included only dementia residents	Nursing homes	Fourteen studies on drug discontinuation, 11 studies on the impact of medication review, using tools such as beers criteria or START/STOPP, six studies on educational programs Other interventions included two case conferences, two comprehensive geriatric assessments, two outreach visits, one ADE profiling, one alternative therapy, two health technologies and informatics	The main limitations contributing to risk of bias were related to detection bias, as blinding of the residents and intervention/health care providers was not possible because of the nature of the intervention
Page et al [15]	N = 21 165 records after duplicates removed, 132 full-text papers reporting 116 studies (132 references) included in the review	Fifty-six RCTs, with 17 428 participants, 22 comparative studies with concurrent control group, with 14 522 participants, 37 comparative studies without concurrent control group, with 2207 participants Mean follow-up = 15.5 (SD = 17.4 months)	N = 34 143, mean age 73.8 (SD = 5.4) years, 51.8% male, mean age > 80 years in 38 studies (4833 people) N = 33 studies included people with dementia (6090 people)	Fourteen studies in hospital, 29 in residential aged care, 73 community based One study included participants in the community and residential aged care, and another was based in the community and hospital	Deprescribing one medication, which could be a single medicine (N = 34 studies), a medicine from a single class (N = 5 studies) or a medicine of a therapeutical category (*N* = 27 studies), withdrawing two medications (N = 11 studies) Deprescribing polypharmacy (3+ therapeutical classes) N = 21 studies, of which N = 18 were patient-specific interventions (N = 11 led by doctors, N = 2 led by pharmacists, N = 1 led by nurses and N = 1 led by multidisciplinary teams)	18/56 (32%) RCTs were rated low risk of bias in at least 4/7 parameters; 68% of RCTs had unclear or high risk of bias Results for non-RCTs not reported

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Study	Number of studies	Study design	Population	Setting	Interventions/exposure	Risk of bias
					N = 10 were investigator-led interventions (N = 8 on medication reviews with recommendations to the prescriber, N = 3 on educational programmes delivered at residential aged care facilities to nurses (N = 1) or to the prescribing doctors (N = 2)	
Rankin et al [16]	N = 7526 records after duplicates removed, 32 studies (including 12 from the previous update) included in the review (18 RCTs, 10 cluster RCTs, four nonrandomised controlled)	Thirty-two studies: 18 RCTs, 10 cluster RCTs, two non-RCTs, two controlled before-after studies, involving 28 672 older people	Mean age of 72.8 years, all study participants had more than one long-term medical condition On average, participants were receiving more than four medicines at baseline (average 8.9 medicines at baseline)	Sixteen studies in hospital settings, three in hospital outpatient clinics, one at the hospital/homecare interface, 12 in an inpatient setting, 10 in primary care and six in nursing homes	Thirty-one studies examined complex, multifaceted interventions of pharmaceutical care in a variety of settings One unifaceted study examined computerised decision support provided to GPs in their own practices	Assessments using the Cochrane Risk of bias tool found that there was a high and/or unclear risk of bias across a number of domains Based on the GRADE approach, the overall certainty of evidence for each pooled outcome ranged from low to very low
Redmond et al [17]	N = 13 585 records after duplicates removed (25 RCTs in total, 22 included in the meta-analyses)	Twenty-five RCTs involving 6995 participants	The mean age of participants was 66.1 years Most studies recruited participants prescribed multiple medications	All of the studies were conducted in hospital or immediately related settings	All studied interventions were classified as "organisational"' according to EPOC taxonomy and were either provider orientated or structural Twenty-three studies were provider orientated (pharmacist mediated) and two were structural (an electronic reconciliation tool and medical record changes)	There were no major differences in the risk of bias of studies included in the review, with 24 studies being judged at high risk for at least one risk of bias domain The GRADE evidence varied from moderate to low or very low reliability

Data extraction on the results of the systematic reviews (outcomes)

Data extraction on the results of the systematic reviews (outcomes)

Study	Outcomes: mortality	Outcomes: adverse drug effects	Outcomes: health, quality of life, resources	Outcomes: evidence on the number of medicines
Jokanovic et al [12]	Not an outcome		Polypharmacy associated with an increased risk of hospitalisation (adjusted for confounders, n = 1), ADRs over 1 year follow-up (unadjusted, n = 1) and falls over a period of 6 months (unadjusted, n = 1); the association with increased risk of falls was diminished in the adjusted analysis	Mean number of medications ranged from 3.8 to 16.6 per resident; median ranged from 4 to 14 Prevalence of polypharmacy varied by definition: 80-88% on 4+ medicines (n = 2), 38-91% on 56 (n = 11), 46-69% on 6+ (n = 3), 19-47% on 7+ (n = 2), 13-75% on 9+ (n = 13), 11-65% on 10+ (n = 11), 4-50% on 12+ (n = 2) Polypharmacy was significantly associated with higher Charlson comorbidity index scores (n = 2), circulatory diseases (n = 3), endocrine and metabolic disorders (n = 3), neurological motor dysfunctioning (n = 3) and some specific symptoms (n = 2), recent discharge from hospital (n = 2) and greater number of prescribers servicing the LTCF (n = 2) Inverse association with age (n = 5) cognitive impairment (n = 3), disability in activities of daily living (n = 3) and length of stay in the LTCF (n = 3)
Leelakanok et al [14]	MA of discrete polypharmacy: 1 additional medicine has a risk ratio of 1.08 [1.04;1.12], *I*-squared = 54% Polypharmacy as 1-4 medicines, risk ratio = 1.24 [1.10; 1.39], *I*-squared = 78% Polypharmacy as 5+ medicines, risk ratio = 1.31 [1.17; 1.47] *I*-squared = 97% Polypharmacy as 6-9 medicines, risk ratio = 1.59 [1.36; 1.87], *I*-squared = 39% Polypharmacy as 10+ medicines, risk ratio = 1.96 [1.42; 2.71], *I*-squared = 99% Results consistent across healthcare setting in studies examining polypharmacy as discrete number of medicines or as <10 medicines, but higher association in people in institutions (although small sample size) Results consistent across different measures of risk	Not an outcome	Not an outcome	Not an outcome

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Study	Outcomes: mortality	Outcomes: adverse drug effects	Outcomes: health, quality of life, resources	Outcomes: evidence on the number of medicines
Clyne et al [8]	Not an outcome	One study found no significant effect on adverse drug effects from a pharmacist intervention	Three pharmacist intervention studies found no significant effect on psychosocial outcome of quality of life with SF-36, one study found a significant decrease in the SF-36 domains of emotional role and social functioning, which was attributed to the high withdrawal rate of pharmacists in the study, one multifaceted intervention had no significant effect on psychological health (12-item well-being questionnaire) Health service use was assessed in two studies, with one reporting a reduction in hospitalisations but not in A&E visits Two studies conducted economic evaluations: one study found that shared pharmaceutical care and written feedback had modest savings regarding medication costs (not statistically significant), and data analysis is ongoing in the second study	The primary outcome was medication appropriateness Four of six organizational interventions reported a reduction in PIP, particularly through pharmacists conducting medication reviews (three of four studies on pharmacists interventions) Evidence of the effectiveness of multidisciplinary teams was weak Both of the two professional (targeting prescriber's directly) interventions were computerised clinical decision support interventions and were effective in decreasing new PIP but not existing PIP Three of four multifaceted approaches were effective in reducing PIP
Hill-Taylor et al [9, 10]	2013: In one study (Gallagher 2011) all-cause mortality was lower in the intervention group, but differences were not statistically significant (5.3% of the intervention group and 7.3% of the control group died, $P = 0\ 414$) 2016: One RCT (Gallagher 2011) was not powered to discover mortality differences between groups	2013: The STOPP criteria identified more medications associated with adverse drug events than the 2002 version of the Beers criteria Patients with PIP, as identified by STOPP, had an 85% increased risk of adverse drug events in one study (Hamilton 2011) (OR = 1 85, 95% CI: 1 51-2 26; $P < 0\ 001$) 2016: Not reported	2013: Research involving the application of STOPP/START on the impact on the quality of life was not found 2016: One RCT (Frankenthal 2014) did not report a difference in quality of life Resource use: One study found lower primary care visits in the intervention group	2013: There was limited evidence that the application of STOPP/START criteria optimised prescribing. Three studies examined the direct costs of PIP in the Republic of Ireland: €188 per patient per year in 2007 (Barry et al[40]), €318 per patient per year in 2007 (Cahir et al[42]) and €263 per patient per year (Byrne et al[49]) Predictors of PIP were reported in nine studies older age, female sex, polypharmacy, comorbidities 2016: Improvement in potentially inappropriate medication rates after intervention, four RCTs, OR 2.98 (random effects; 95% CI 1.30, 6.83; *I*-squared = 86.7%; three RCTs (excluding outlier Gallagher 2011), OR 1.98 (random effects; 95% CI 1.16, 3.40; *I*-squared = 64.3%)

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Study	Outcomes: mortality	Outcomes: adverse drug effects	Outcomes: health, quality of life, resources	Outcomes: evidence on the number of medicines
Johansson et al [11]	The strategies to reduce polypharmacy had no effect on all-cause mortality (all studies: odds ratio 1.02; 95% CI 0.84, 1.23; RCTs only: OR 1.05, 95% CI 0.85, 1.29) *I*-squared values for statistical heterogeneity were 8% for all studies and 12% for just RCTs	None of the included studies analysed the effect on new morbidity, ADR, adverse events after discontinuation of drugs or process of care	Overall, the effects of interventions on the predefined secondary outcomes were minimal Hospitalisations: 11/25 studies reported hospitalisation as an outcome measure, two studies found a significant effect of the intervention on hospitalisation, one study found a reduction in the unplanned readmission and the other found a reduction in the length of stay, five studies assessed all-cause hospital admissions and found no significant differences	Twenty-three studies provided data on the number of prescribed drugs and two studies included prescribed and over-the-counter drugs The weighted mean number of drugs at baseline was 7.4 drugs per patient in both groups; at follow-up, the weighted mean number of drugs was reduced by 0.2 in the intervention group but increased by 0.2 in the control groups; it was not possible to calculate confidence interval Three studies found significant reduction in a between-group analysis
Kua et al [13]	Across 26 RCTs (12 248 residents) deprescribing reduced mortality rates (fixed effect: odds ratio 0.90, 95% CI 0.82, 0.99) However, in the subgroup analysis by intervention type, only medication review-directed deprescribing interventions (fixed effect: eight RCTs, 6 115 residents) was statistically significant (OR 0.74, 95% CI 0.65, 0.84) When a random-effects model was applied, statistically significant differences were not evident (all interventions, OR 1.02 95% CI 0.85, 1.23; medication review, OR 0.83 95% CI 0.64, 1.07) *I*-squared values for statistical heterogeneity were 51% for all interventions and 48% for medication review Subgroup analysis performed by the authors found that studies conducted in Australia found greater beneficial effects (OR = 0.66, 95% CI 0.5-0.77) as well as deprescribing by multiple drug classes (OR = 0.89, 95% CI 0.81-0.98)	Fourteen studies examined drug discontinuation by doctors, two studies by pharmacists and one study by nurses; 86% of studies targeted psychotropic drugs Generally, the careful discontinuation of antipsychotics and diuretics had negligible adverse effects on psychiatric and cardiovascular outcomes, respectively	Ten studies (n = 6905 people) examined the number of people who fell after the intervention, with most reporting no difference with the exception of one study Pooling of eight analysable studies (n = 3343 people) suggested that deprescribing interventions did not significantly reduce the number of people who had falls, with a significant result in the subgroup analysis by medication review-directed (OR = 0.76, 95% CI 0.62-0.93) Eight studies (7863 residents) examined hospitalisation rates after the intervention, and most found no difference; meta-analysis of four analisable studies (n = 1002) found a nonsignificant reduction in the number of hospitalised residents (OR = 0.72, 95% CI 0.31-1.66)	Five studies (2092 people) reported PIMS after the intervention period, according to various criteria All studies found a significant reduction in PIMs; the meta-analysed OR for the odds of people having PIMS was 0.41 (95% CI 0.19-0.89) from three analysable studies (1711 people)
Page et al [15]	Polypharmacy as deprescribing target: 10 RCTs (3151 patients): OR = 0.82 (0.61; 1.11); *I*-squared = 23%; educational	Single studies on polypharmacy, glucosamine, carbamazepine, antidepressants, benzodiazepine,	Large number of outcomes, largely disease-specific	Deprescribing polypharmacy reduced the total number of medicines (MD = −0.99 [−0.93; −0.14]) in two studies and the

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Study	Outcomes: mortality	Outcomes: adverse drug effects	Outcomes: health, quality of life, resources	Outcomes: evidence on the number of medicines
	programmes have a OR = 1.21 (0.86; 1.69) whereas investigator led has OR = 0.62 (0.43; 0.88); subgroup analysis by age had similar results, aged 80+ OR = 0.88 (0.58; 1.34) (as per forest plot), aged 65-79 years OR = 0.64 (0.40; 1.04); similar results by presence of dementia (0.89 [0.63; 1.27] with *vs* 0.64 [0.36; 1.13] without) Nonrandomised studies on mortality (OR = 0.32 [0.17; 0.60], N = 2) Studies on deprescribing single/classes medicines did not find a stats significant difference on mortality odds Beta-blockers (N = 1 RCT; OR = 1.14 [0.35; 3.72]), diuretics (N = 2 RCT, OR = 3.21 [0.96; 10.70]), statins (N = 1 RCT, OR = 0.87 [0.58; 1.31]), bisphophonates (N = 2 RCT, OR = 1.02 [0.46; 2.26]), carbamazepine (N = 1 RCT, OR = 0.28 [0.01; 7.33]), antidepressants (N = 2 RCT, OR = 1.13 [0.47; 2.69]), antipsychotics (N = 5 RCT, OR = 0.59 [0.33; 1.07]), benzodiazepines (N = 1 RCT, OR = 0.10 [0.01; 1.93]), anticholinesterease inhibitors (N = 2 RCT, OR = 4.63 [0.93; 23.12]), ICS (N = 1 RCT, OR = 0.14 [0.01; 2.67]).	prednisolone, ICS); three studies on antipsychotics Heterogeneous results The authors note that neither deprescribing to reduce polypharmacy nor deprescribing targeting single medicines were not associated with a significant risk in adverse drug withdrawal events	Quality of life assessed with a variety of measures, including (but not restricted to) EQ-5D utility and SF-36 The authors noted that in respect to deprescribing of polypharmacy, there was no change in the incidence of adverse drug events, in cognitive function or the risk of falls; there was a statistically significant reduction in the number of falls (MD = −0.11 [−0.21; −0.02]; 844 participants; three studies) The authors noted that deprescribing to reduce polypharmacy was not associated with significant changes in quality of life, although there was evidence of a reduction in the decline in quality of life (MD = 0.03 [0.01; 0.06], 189 patients, one study) In respect to deprescribing of single medicines, there were some changes in relevant outcomes, specifically increase in blood pressure when antihypertensive drugs were prescribed (eg, increase in 9.73 mm Hg in systolic blood pressure with deprescribing of diuretics)	number of PIMs (MD = −0.49 [−0.70; 0.28]) in three studies Inconsistent effect depending on the type of class/medicine
Rankin et al [16]	Not an outcome	Medication-related problems were reported in eight studies (N = 10 087) using different terms (eg, adverse drug reactions, drug-drug interactions) No consistent intervention effect on medication-related problems was noted across studies	In one study participants in the intervention group experienced an increased QoL, in one study there was a decline in QoL in both the intervention and control groups, and in 10 studies no changes in QoL were detected Pharmaceutical care may make little or no difference in hospital admissions (two studies)	It is uncertain whether pharmaceutical care improves medication appropriateness (as measured by an implicit tool) (MD -4.76, 95% CI -9.20 to −0.33), reduces the number of PIMs (SMD −0.22, 95% CI −0.38 to −0.05), reduces the proportion of patients with one or more PIMs (RR 0.79, 95% CI 0.61-1.02), reduces the proportion of patients with one or more PPOs (RR 0.40, 95% CI 0.18-0.85) Pharmaceutical care may slightly reduce the number of PPOs (SMD −0.81, 95% CI −0.98 to −0.64 (two studies)

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Study	Outcomes: mortality	Outcomes: adverse drug effects	Outcomes: health, quality of life, resources	Outcomes: evidence on the number of medicines
Redmond et al [17]	One study reported no difference in mortality (RR 0.75, 95% CI 0.27-2.08)	One study reported potential ADEs; defined as being due to discrepancies, three studies described an outcome of PADEs or ameliorable ADEs calculated using the bates methodology to retrospectively identify medication-related ADEs with no certainty of whether reconciliation reduced PADEs or nonadherence, four studies reported reconciliation may make little or no difference to ADEs (RR 1.09, 95% CI 0.91-1.30; *I*-squared = o%)	Reconciliation also had little or no effect on PADEs (RR 0.37. 95% CI 0.09-1.57; three studies; *I*-squared = 84%) or on ADEs (RR 1.09, 95% CI 0.91-1.30; four studies; *I*-squared = 0%) Evidence of the effect of the interventions on healthcare utilisation was conflicting and had an uncertain effect on a composite measure of hospital utilisation (emergency department, rehospitalisation RR 0.78, 95% CI 0.50-1.22; four studies; *I*-squared = 48%)	Twenty studies comparing medication reconciliation interventions to standard care of participants with at least one medication discrepancy showed RR 0.53 (95% CI 0.42-0.67; *I*-squared = 91%) Reconciliation's effect on the number of reported discrepancies per participant was also uncertain (MD −1.18, 95% CI −2.58-0.23; four studies; *I*-squared = 96%), as well as its effect on the number of medication discrepancies per participant medication (RR 0.13, 95% CI 0.01-1.29; two studies; *I*-squared = 98%)

[a]A&E, ; ADEs, adverse drug events; ADR, CI, EPOC, GRADE, ICS, LTCF, MAI, MD, mean difference; PADES, preventable adverse drug events; PIMs, potentially inappropriate medications; PIP, PPOs, potential prescribing omissions; QoL, RCT, RR, ; SMD, standardised mean difference.
[b]Data extraction on the conclusions of the included systematic reviews

Data extraction on the conclusions of the included systematic reviews

Study	Conclusions of the systematic review	Limitations as reported by the authors	Areas for future research suggested by the authors
Jokanovic et al [12]	The prevalence of polypharmacy in residents in LTCFs is high, but varies widely between LTCFs and depending on the definition of polypharmacy. The factors positively associated with polypharmacy are comorbidity, recent hospital discharge, number of prescribers; inversely associated are older age, cognitive impairment, ADL disability and length of stay in LTCF.	Not all relevant studies may have been picked up by the searches due to restrictions due to language (English) and date (year 2000+). Clinical appropriateness was not assessed in this review. No meta-analysis performed, which was due to the heterogeneity in the included studies.	Future studies should use consistent definitions of polypharmacy, have a longitudinal design and collect information on factors that may influence the exposure to polypharmacy and health outcomes.
Leelakanok et al [14]	Polypharmacy is associated with higher mortality risk, and relationship is dose-dependent (higher mortality risk for more medicines).	Risk of exposure misclassification in the included studies, given that some studies did not provide detailed information on the medicines and/or collected information from self-report or surveys. Risk of confounding bias in that the association between polypharmacy and mortality may not be causal. Focus on mortality, when drugs may be prescribed to improve QoL with known increased risk of mortality (eg, opioids in palliative care). Heterogeneity in the definition of polypharmacy.	Not discussed.

(Continues)

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Study	Conclusions of the systematic review	Limitations as reported by the authors	Areas for future research suggested by the authors
		Exclusion of studies due to lack of data to calculate a risk ratio for the association.	
Clyne et al [8]	Interventions including organisational (pharmacist interventions), professional (computerized clinical decision support systems) and multifaceted approaches appear beneficial in terms of reducing PIP, but the range of effect sizes reported was modest, and it is unclear whether such interventions can result in clinically significant improvements in patient outcomes.	Meta-analysis could not be undertaken due to heterogeneity, few studies conducted process evaluations or presented adequate detail to allow for an analysis, studies did not describe usual care in adequate detail, potential biases limited studies, particularly in relation to selection bias and only half of the studies had adequate sample size.	Although the interventions appear to have been beneficial in terms of reducing PIP, the clinical effect this may have on outcomes such as ADEs and QoL is unknown. Future research should consider involving individuals to explore their preferences in relation to PIP and interventions to decrease it and explore whether the differences in decreasing the initiation of PIP, as opposed to the discontinuation of existing PIP, results from differences in the interventions or differences in applying explicit or implicit criteria.
Hill-Taylor et al [9, 10]	2013: The STOPP/START criteria appear to be more sensitive than the 2002 version of the beers criteria. Limited evidence was found related to the clinical and economic impact of the STOPP/START criteria 2016: STOPP/START may be effective in improving prescribing quality, clinical, humanistic and economic outcomes.	2013: Although referred to as "STOPP" or "START", some researchers used versions of the criteria that had been modified for their jurisdictional prescribing practices or formularies and in some instances were shortened. Not all researchers had access to complete medication profiles including over-the-counter medications. No study indicated an attempt to document or evaluate adherence. Researchers who had used pharmacy claims data were only able to confirm that patients had made a claim for medications, not that they have actually taken them 2016: Three of the studies had populations that were restricted to a single facility and interventions performed in the included studies varied in implementation, populations, outcomes and duration.	2013: To date, the clinical, humanistic and economic impacts of the application of the STOPP/START criteria have not been well explored 2016: Additional research investigating STOPP/START is needed, especially in frail elderly and community-living patients receiving primary care.
Johansson et al [11]	There is no convincing evidence that the strategies assessed are effective in reducing polypharmacy or have an impact on clinically relevant endpoints.	The quality of the evidence assessed using GRADE on strategies to reduce polypharmacy was rated as low to very low, and any estimate of effect is very uncertain. There was insufficient evidence on the effect of strategies to reduce polypharmacy on patient relevant outcomes such as mortality and hospitalisation.	There is a need to develop more effective strategies to reduce inappropriate polypharmacy and to test them in large, pragmatic randomised controlled trials on effectiveness and feasibility. When addressing polypharmacy, research groups should clearly define their methodology regarding the assessment of medication appropriateness, and they should also focus on clinically relevant outcomes such as mortality or hospital admissions.
Kua et al [13]	Compared to other deprescribing interventions, medication review directed deprescribing had significant benefits on older residents in nursing homes.	There was limited evidence to show that deprescribing was effective in reducing all-cause mortality, number of fallers, as well as hospitalization rates. However, when the deprescribing activity involved a medication review by healthcare professionals in a	Further studies are needed to fully ascertain the health benefits of medication reviewed directed deprescribing practice.

(Continued)

Study	Conclusions of the systematic review	Limitations as reported by the authors	Areas for future research suggested by the authors
		structured and active way, it significantly reduced both all-cause mortality and number of fallers, compared to other types of deprescribing interventions.	
Page et al [15]	Deprescribing appears to be feasible and safe. There is no evidence of an increased risk of adverse outcomes and some evidence of greater likelihood of positive health outcomes. Overall, RCTs found no effect of deprescribing interventions had on mortality risk, although patient-specific interventions in particular had a significant reduction on mortality risk. Health outcomes varied by target medication for withdrawal and include a reduction in the number of falls and increase in blood pressure. Deprescribing is feasible. Concluded that deprescribing should be routinely considered for older people.	Language bias, inclusion of nonrandomised studies and small RCTs with low quality, inclusion of studies that aimed to assess the feasibility of deprescribing intervention, heterogeneity in follow-up, settings and patients' characteristics.	Large RCTs on patient-specific deprescribing interventions to confirm the findings of the review. Research to understand which medications should be prescribed in whom and at what point in time.
Rankin et al [16]	It is unclear whether interventions to improve appropriate polypharmacy, such as reviews of patients' prescriptions, resulted in clinically significant improvement, but they may be slightly beneficial in terms of reducing PPOs, but this effect estimate is based on only two studies, which had serious limitations in terms of risk bias.	The meta-analysis based on the number of PPOs per participant comprised just two studies. This limits the value of any pooled effect estimate. Based on observed heterogeneity in the pooled effect estimates, the findings of meta-analyses (medication appropriateness as measured by an implicit tool), the number of PIMs and proportion of patients with one or more PIMs or PPOs should be treated cautiously, as the interventions did not seem to work consistently across all studies. Furthermore, the certainty of evidence presented in this review, as described by the GRADE approach, remains low or very low.	Further research should attend to rigour in study design. More research is needed to test whether existing tools for comprehensive medication review can improve appropriate polypharmacy.
Redmond et al [17]	The impact of medication reconciliation interventions, in particular pharmacist-mediated interventions, on medication discrepancies is uncertain due to the certainty of the evidence being very low. There was also no certainty of the effect of the interventions on the secondary clinical outcomes of ADEs, PADEs and healthcare utilisation.	Meta-analysis of the primary outcomes showed a high degree of statistical heterogeneity and low certainty of evidence, making it difficult to have any certainty of the effect of the interventions.	Further work is required to develop a consensus on identifying, defining, measuring and reporting discrepancies. Future studies should utilise clear definitions of discrepancies as well as objective measurement techniques and appropriate choice of time points attendant to the transition point at which the intervention is applied.

[a]ADR, adverse drug reaction; CI, confidence interval; EPOC, Effective Practice and Organisation of Care; GRADE, Grading of Recommendations Assessment, Development and Evaluation; ICS, inhaled corticosteroids; LTCF, long-term care facility; MAI, Medicines Appropriateness Index; MD, mean difference.

APPENDIX 3: STUDIES EXCLUDED AT THE FULL-TEXT STAGE WITH REASON

AMSTAR-2 quality assessment judgements for exclusion ("yes" required for all domains for inclusion)

Study (to reorder once referenced)	Reason for exclusion
Clyne et al[56]	Did not meet quality assessment criteria for inclusion
Gutierrez Valencia et al[57]	Did not meet quality assessment criteria for inclusion
Tani et al[58]	Did not meet quality assessment criteria for inclusion
Thillainadesan et al[59]	Did not meet quality assessment criteria for inclusion
Tija et al[60]	Did not meet quality assessment criteria for inclusion
Disalvo et al[61]	Not a topic of interest
Palmer et al[62]	Not a topic of interest
Patton et al[63]	Not a topic of interest
Piraino et al[64]	Not a topic of interest
Stewart et al[65]	Not a question of interest
Thompson et al[66]	Not a question of interest
Ulley et al[67]	Not a question of interest

Study	Topic	Comprehensive search strategy	Duplicate data extraction	Quality assessment	Study description
Clyne et al[56]	Effectiveness of interventions to reduce PP	Yes	Cannot tell	Cannot tell	Yes
Gutierrez Valencia et al[57]	Effectiveness of interventions to reduce PP	Yes	Yes	Cannot tell	Yes
Tani et al[58]	Effectiveness of interventions to reduce PP	Yes	Cannot tell	No	Yes
Thillainadesan et al[59]	Effectiveness of interventions to reduce PP	Yes	No	Yes	Yes
Tija et al[60]	Effectiveness of interventions to reduce PP	Yes	Yes	No	Yes

[a]PP, problematic polypharmacy.